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Pretreatment blood pressure reliably predicts progression of chronic nephropathies

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Background. Random, nontimed blood pressure (BP) measurements in the outpatient clinic may fail to provide reliable information on actual daily BP control in renal patients on chronic antihypertensive therapy.

Methods. In a cohort of 163 patients with proteinuric chronic nephropathies followed prospectively with repeated BP and glomerular filtration rate (GFR) measurements, we compared baseline and follow-up pretreatment, morning ("trough," measured by standard procedures, and "0 minutes," measured by an automatic device) and post-treatment (120 minutes) measurements, with BP monitored up to 600 minutes after treatment administration. We then evaluated which BP value most reliably predicted GFR decline (ΔGFR) and progression to end-stage renal failure (ESRF) over a median (interquartile range) follow-up of 20 (9 to 25) months.

Results. GFR decline was more reliably predicted by systolic as compared with diastolic BP and by pretreatment as compared to post-treatment BP, regardless of the timing and method of measurement, respectively. In particular, at the 120-minute baseline and follow-up measurements, systolic BP had no predictive value in patients with less severe renal insufficiency and baseline diastolic BP, regardless of the level of renal dysfunction. The BP predictive value was remarkably higher in ramipril than in conventionally treated patients. All follow-up—but no baseline—measurements reliably predicted the risk of ESRF in the entire study group.

Conclusions. In patients with progressive chronic nephropathies, systolic BP and pretreatment morning BP measurements are the most reliable predictors of disease outcome and may serve to guide antihypertensive therapy in routine clinical activities and in prospective controlled trials, particularly in patients on angiotensin-converting enzyme inhibitor therapy. Reliability and relevance of single measurements taken at different times after treatment administration are questionable.

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Progressive renal function deterioration occurs in most forms of chronic nephropathy [1]. A recognized major determinant of renal injury in these circumstances is arterial hypertension: the higher the levels of arterial blood pressure (BP), the greater the risk of a given patient to develop renal failure in the long term [2, 3]. On the other hand, many clinical studies are available indicating that BP reduction is protective [reviewed in 4]. In most intervention trials aimed at evaluating the effect of different antihypertensive regimens on disease progression to renal failure, reported values of arterial BP were random measurements in outpatient clinics, which may lead to different results depending on the time BP is measured [5–8]. Actually, in some studies, BP was measured in the morning just before the administration of antihypertensive medication, when the residual effect of treatment is minimal ("trough" BP) [9–11]. In a few others, the BP was measured shortly after the administration of the antihypertensive treatment, conceivably when the medication has achieved the peak effect [12]. However, most of the studies did not report the timing of BP measurements [5–8], which renders data interpretation even more difficult. One also has to take into account that random measurements in the outpatient clinic do not distinguish sustained hypertension from "white-coat hypertension" and, even more important, fail to provide information on daily response to medication [13].

In the 352 patients with proteinuric chronic nephropathies enrolled in the Ramipril Efficacy In Nephropathy (REIN) trial [9–11], the diastolic BP was reduced at comparable levels by conventional antihypertensives or by the angiotensin-converting enzyme (ACE) inhibitor ramipril in a randomized, double-blind design aimed to

test the hypothesis that protein traffic and its reduction by an ACE inhibitor influenced renal disease progression [9]. In all patients, "trough" BP was measured by a standard sphygmomanometer in the morning, after five minutes of rest in the sitting position, and mean values of three consecutive measurements two minutes apart were recorded. A subgroup of patients, however, during the occasion of glomerular filtration rate (GFR) measurements, had their BP also measured by an automatic device from the time the "trough" value was taken ("time 0") up to 10 hours after treatment administration. This allowed a comparison of the BP values taken at different times—regardless of the adopted method of measurement—and to evaluate which of them more reliably predicted disease progression and response to treatment. By this approach, we also had the unique opportunity to monitor and compare BP response to ACE and non-ACE inhibitor therapy in a large cohort of patients with chronic progressive nephropathies and different degrees of renal dysfunction. The results of these post hoc analyses form the basis of this report.

METHODS

The design of the REIN study has been described in detail elsewhere [9–11]. The protocol was approved by the ethical committee and by the institutional review board of the 14 hospitals involved. Every patient gave written informed consent. The primary study objectives were to assess the effects of treatment with ramipril on ΔGFR and time to end-stage renal failure (ESRF). Secondary objectives were to assess the long-term effects of treatment with ramipril on the degree of proteinuria and incidence of major cardiovascular complications, and the total and cardiovascular mortality rates.

Patients and definitions

Study participants were normotensive or hypertensive patients of both sexes, between 18 and 70 years old, with chronic nephropathy and persistent proteinuria, who had not received ACE inhibition therapy for at least two months or any treatment with corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or immunosuppressive drugs for at least six months. Chronic nephropathy was defined as creatinine clearance in the range of 20 to 70 mL/min/1.73 m^2 with a variation of less than 30% in the three months prior to screening evaluation. Persistent proteinuria was defined as urinary protein excretion $\geq$1 g/24 hours from at least three months without evidence of urinary tract infection or overt heart failure (New York Heart Association Class III or more). A detailed description of the exclusion criteria has been given elsewhere [9–11].

Study design

Following screening evaluation, all eligible patients entered a one-month, single-blind, placebo run-in phase. Patients were given one placebo capsule daily and were asked to return to the hospital after 15 and 30 days for the measurement of BP, creatinine clearance, and 24-hour urinary protein excretion, and to evaluate routine hematochemistry, complete blood cell count, and tablet compliance. On day 15, the GFR was determined by the plasma clearance measurement of unlabeled iohexol [14]. Patients with a creatinine clearance of 20 to 70 mL/min/1.73 m^2, urinary protein excretion $\geq$1 g/24 hours, serum potassium concentration 3.5 to 5 mEq/L, and tablet compliance >80% (means of the determinations at day 15 and at day 30) entered the randomized double-blind phase of the study. According to mean urinary protein excretion at day 15 and at day 30, patients were stratified into two strata: stratum 1:>1 and <3 g/24 hours and stratum 2:$\geq$3 g/24 hours.

At the end of the placebo run-in phase, in each center, the patients were randomly assigned to receive 1.25 mg capsules of ramipril or placebo (identical appearance) on a 1:1 basis within each stratum. The dose of the study drugs was titrated upward every two weeks to 2.5 or 5 mg/day of ramipril or placebo until diastolic BP was reduced below 90 mm Hg. Antihypertensive agents (but not ACE inhibitors) were introduced, and their doses were adjusted whenever appropriate to achieve and maintain diastolic BP <90 mm Hg. In patients already treated with antihypertensive agents, the dose of the study drugs was titrated upward, and the dose of other antihypertensives progressively reduced to avoid symptomatic hypotension. In each patient, the general goal was to adjust the dose of the study drugs in order to achieve and maintain the target BP with the minimum dose of concomitant antihypertensive agents. ACE inhibitors or angiotensin II receptor antagonists could not be added to the study drugs throughout the whole study period.

All of the patients were recommended to limit their sodium intake and to eat 0.6 to 0.8 g/kg/day of protein per kilogram of body weight per day. No change in the diet was then introduced during the study. Dietary compliance was assessed by evaluating 24-hour urinary sodium and urea excretion.

At randomization, every month during the first three months, and every three months thereafter, each patient was examined by a physician. At each examination, BP and heart rate were measured in sitting position in the morning (8 to 9 a.m.), immediately before the ingestion of the drug ("trough" BP), and serum creatinine and electrolyte concentrations, other serum biochemical values (uric acid, glucose, cholesterol, triglycerides, liver enzymes, and bilirubin), and a complete blood count

were determined, as well as 24-hour urinary protein, sodium, and urea excretion. The GFR was measured at months 1, 3, and 6 after randomization and every six months thereafter. On each occasion, a fixed dose of iohexol was injected immediately after the study drug administration. To calculate the plasma clearance of iohexol, blood samples were taken immediately before the injection of iohexol (time, 0 minute) and at predetermined times thereafter: In patients with a baseline creatinine clearance ≥45 mL/min/1.73 m^2, blood samples were taken at 120, 150, 180, 210, and 240 minutes; in those with baseline creatinine clearance <45 mL/min/1.73 m^2, blood samples were taken at 120, 180, 240, 300, 360, 450, and 600 minutes after the iohexol injection.

Blood pressure measurements

On the occasion of each GFR measurement, all patients attending the Clinical Research Center for Rare Diseases "Aldo & Cele Daccò" had their BP measured by a standard sphygmomanometer in the morning (8 to 9 a.m.) shortly before study drug administration ("trough" BP). The trough value was the mean of three consecutive measurements taken at the dominant arm two minutes apart with the patient in a sitting position. Immediately after trough BP was measured, the cuff of an automized device (Kolormon TM 7250; Kontron Instruments, Munchen, Germany) was applied to the dominant arm, and the BP was measured with the patient still in the sitting position ("time 0" BP). Antihypertensive treatment, including the study medication, was then administered. Then additional BP measurements were taken by the automatic device with the patient in the sitting position one minute before each blood sample collection during each GFR measurement (0 to 240 minutes or 0 to 600 minutes for patients with baseline creatinine clearance ≥ or <45 mL/min/1.73 m^2, respectively). The BP measured by the automatic device and averaged throughout each GFR measurement was defined as "monitored" BP. The measurement taken by the automatic device at 120 minutes after treatment administration ("120-minute" BP) was selected among post-treatment measurements for comparisons with trough, time 0, and monitored BP. Similar comparisons were done also for all the other post-treatment automatic measurements (data not shown). All BP values (trough, time 0, 120 minutes, and monitored) were taken either at study entry (that is, at randomization, before any study treatment administration) and throughout the entire study period (that is, during the occasion of each GFR measurement) and were therefore referred to as "basal" or "follow-up" BPs, respectively. Average follow-up BPs were the trough, time 0, 120 minutes, and monitored BPs taken at each GFR measurement (including baseline) and averaged throughout the entire study period.

Patients who entered the REIN study, but who did not attend the Clinical Research Center and did not have their BP measured by either a standard sphygmomanometer or an automatic device were not included in data analyses.

Outcome measures

Outcome measures were ΔGFR, time to ESRF, and 24-hour urinary protein excretion rate (measured by the biuret precipitation method in all participating centers). To estimate the rate of GFR decline, a minimum of three GFR measurements per patient (including baseline) were required.

Statistical analysis

Data were analyzed on an intention-to-treat basis. Dichotomous and polychotomous baseline characteristics were compared with Fisher's exact test; continuous baseline characteristics were compared with the Wilcoxon rank-sum test. The primary analysis on the decline in GFR was carried out in patients who had three or more renal function determinations. A single-slope linear model was used, and slopes were compared by Wilcoxon rank-sum test. For the analysis of the length of time to event end points, product-limit life-table distributions were compared with the log-rank statistic. The Pearson *r* correlation coefficient was estimated to summarize the relationship between two continuous variables. Multiple regression and proportional hazards model were used in order to analyze predictors of ΔGFR and time to ESRF prospectively. Trough, 0 minute, 120 minutes, and monitored BPs were included in the analyses. The analyses were performed with Statistical Analysis System software. A P value of less than 0.05 was considered to indicate statistical significance. All statistical tests were two sided. Data are mean ± SD or median and interquartile (IQ) range, unless otherwise stated.

Before performing the previously mentioned analyses, the agreement between the two methods of BP measurement (by standard sphygmomanometer or automatic device) was assessed according to Bland and Altman [15]. Two repeated measures of systolic and diastolic BP were taken by both methods, in a random order, at the dominant arm of 42 subjects. The means of the two measurements by each method in each individual patient were used for assessing agreement. A corrected standard deviation of differences between methods was then calculated [15]. Correlations (r = 0.84, P = 0.0001 vs. 0.77, P = 0.0001) and limits of agreements [standard minus automatic measurements: −4.82 (−26.22 to 16.58) vs. 1.23 (−13.7 to 15.53) mm Hg] between the two methods were calculated either for systolic and diastolic BP, respectively.

Table 1. Clinical characteristics at the time of randomization in the entire study group (Overall) and in patients with a baseline creatinine clearance (C_{Cr}) < or ≥45 mL/min/1.73 m^2 according to randomization to ramipril or conventional treatment

	Overall		C_{Cr} <45 mL/min/1.73 m^2		C_{Cr} ≥45 mL/min/1.73 m^2	
Variable *mean ± SD*[a]	Ramipril (*N* = 86)	Conventional (*N* = 77)	Ramipril (*N* = 31)	Conventional (*N* = 34)	Ramipril (*N* = 55)	Conventional (*N* = 43)
Demographics						
Age *years*	51.7 ± 12.6	49.8 ± 14.9	53.0 ± 10.1	51.8 ± 15.2	51.0 ± 13.9	48.2 ± 14.6
Males *number of patients (%)*	68 (79%)	58 (75%)	24 (77%)	21 (62%)	44 (80%)	37 (86%)
Females *number of patients (%)*	18 (21%)	19 (25%)	7 (23%)	13 (38%)	11 (20%)	6 (14%)
Renal disease						
Glomerular *number of patients (%)*	41 (48%)	30 (39%)	13 (42%)	11 (32%)	28 (51%)	19 (44%)
Interstitial, polycystic *number of patients (%)*	8 (9%)	2 (3%)	4 (13%)	1 (3%)	4 (7%)	1 (2%)
Other, unknown *number of patients (%)*	37 (43%)	45 (58%)	14 (45%)	22 (65%)	23 (42%)	23 (54%)
Renal function						
GFR *mL/min/1.73 m^2*	49.2 ± 20.0	44.5 ± 17.1	30.5 ± 8.0	30.8 ± 11.5	59.8 ± 16.6	55.2 ± 12.6
Creatinine clearance *mL/min/1.73 m^2*	52.5 ± 18.5	49.9 ± 17.9	31.3 ± 8.3	33.3 ± 8.8	64.4 ± 10.0	63.1 ± 10.8
Serum creatinine *mg/dL*	1.99 ± 0.81	2.13 ± 0.82	2.76 ± 0.75	2.74 ± 0.84	1.56 ± 0.42	1.65 ± 0.36
Urinary protein excretion *g/day*[b]	3.23 ± 2.13	2.99 ± 1.97	3.45 ± 2.51	3.34 ± 1.67	3.11 ± 1.90	2.71 ± 2.16
Urinary urea excretion *mmol/day*	23.7 ± 7.0	24.1 ± 7.5	20.2 ± 6.4	20.6 ± 7.8	25.8 ± 6.57	26.8 ± 6.2
Urinary sodium excretion *mmol/day*	196.0 ± 78.7	189.1 ± 73.3	197.8 ± 102.4	186.5 ± 86.4	194.9 ± 62.4	191.2 ± 62.1
Arterial blood pressure						
Systolic *mm Hg*	153.0 ± 17.2	151.9 ± 17.7	155.9 ± 18.6	153.0 ± 17.4	151.4 ± 16.2	151.1 ± 18.1
Diastolic *mm Hg*	94.7 ± 11.3	94.7 ± 12.3	94.8 ± 13.2	93.3 ± 12.0	94.7 ± 10.2	95.8 ± 12.6
Mean *mm Hg*	114.2 ± 12.2	113.7 ± 13.1	115.2 ± 13.6	113.2 ± 12.6	113.6 ± 11.5	114.2 ± 13.6
Lipids and potassium						
Serum cholesterol *mg/dL*	250.5 ± 58.4	246.6 ± 49.1	258.8 ± 52.7	247.2 ± 55.5	246.2 ± 61.2	246.2 ± 44.1
Serum triglycerides *mg/dL*	208.7 ± 190.6	162.7 ± 94.5	216.9 ± 166.3	159.5 ± 87.2	204.2 ± 204.2	165.3 ± 100.7
Serum potassium *mmol/L*	4.56 ± 0.64	4.50 ± 0.57	4.58 ± 0.70	4.74 ± 0.54	4.42 ± 0.68	4.46 ± 0.47

[a] For no parameter differences between ramipril and conventional achieved the statistical significance (for categorical variables the *P* values were based on Fisher's exact test. The *P* values for continuous variables were based on the Wilcoxon test)

[b] Urinary protein excretion is the mean of the last two measurements before randomization

RESULTS

Overall, the present study included 163 of the 352 patients with proteinuric chronic nephropathies involved in the REIN Study [9–11]. Of note, the proportion of patients with nephrotic range proteinuria (41 vs. 47%) or arterial hypertension (88 vs. 84%) and on ramipril or conventional therapy (53 vs. 50%) in the present series and in the whole REIN study group, respectively, was very well comparable. Main clinical and laboratory parameters in the overall study population and in the two subgroups with baseline creatinine clearance <45 or ≥45 mL/min/1.73 m^2 are listed in Table 1. A comparable proportion of patients in the entire study group and within the two subgroups was on ramipril or conventional treatment. Baseline characteristics of ramipril and conventionally treated patients were comparable in the entire study group and within the two subgroups (Table 1).

The course of systolic/diastolic BP monitored during the GFR measurements in ramipril or conventionally treated patients with baseline creatinine clearance <45 or ≥45 mL/min/1.73 m^2, averaged throughout the entire study period, is shown in Figure 1. The corresponding trough systolic/diastolic BP values averaged during the study period in the ramipril and conventional treatment groups were 142.8 ± 14.9/88.8 ± 8.7 versus 145.2 ± 12.8/91.1 ± 8.4 mm Hg, respectively, among patients with creatinine clearance ≥45 mL/min/1.73 m^2, and 147.5 ± 13.2/90.3 ± 7.4 versus 146.1 ± 14.1/91.2 ± 10.0 mm Hg among patients with creatinine clearance <45 mL/min/1.73 m^2. Of note, in both groups, ramipril and conventional treatments achieved a "smooth" BP profile, without remarkable acute BP reductions shortly after treatment administration (Fig. 1). Among patients with a baseline creatinine clearance <45 mL/min/1.73 m^2, systolic (ramipril, 144.0 ± 12.1 mm Hg; conventional, 146.7 ± 15.3 mm Hg) and diastolic (ramipril, 86.3 ± 6.5 mm Hg; conventional, 89.8 ± 8.1 mm Hg) BP measurements averaged throughout the 600-minute monitoring period and at each time point were comparable in the two treatment groups (Fig. 1). In contrast, among patients with baseline creatinine clearance ≥45 mL/min/1.73 m^2, systolic (ramipril, 140.9 ± 13.7 mm Hg; conventional, 147.4 ± 14.1 mm Hg) and diastolic (ramipril, 85.2 ± 1.5 mm Hg; conventional, 90.8 ± 6.1 mm Hg) BPs averaged throughout the 600-minute monitoring period and at each time point tended to be higher in the conventional than in the ramipril group (Fig. 1). However, despite the different response with regards to BP reduction, the two groups of patients with baseline creatinine clearance <45 or ≥45 mL/min/1.73 m^2 had a virtually identical pattern of response to ramipril as compared with conven-

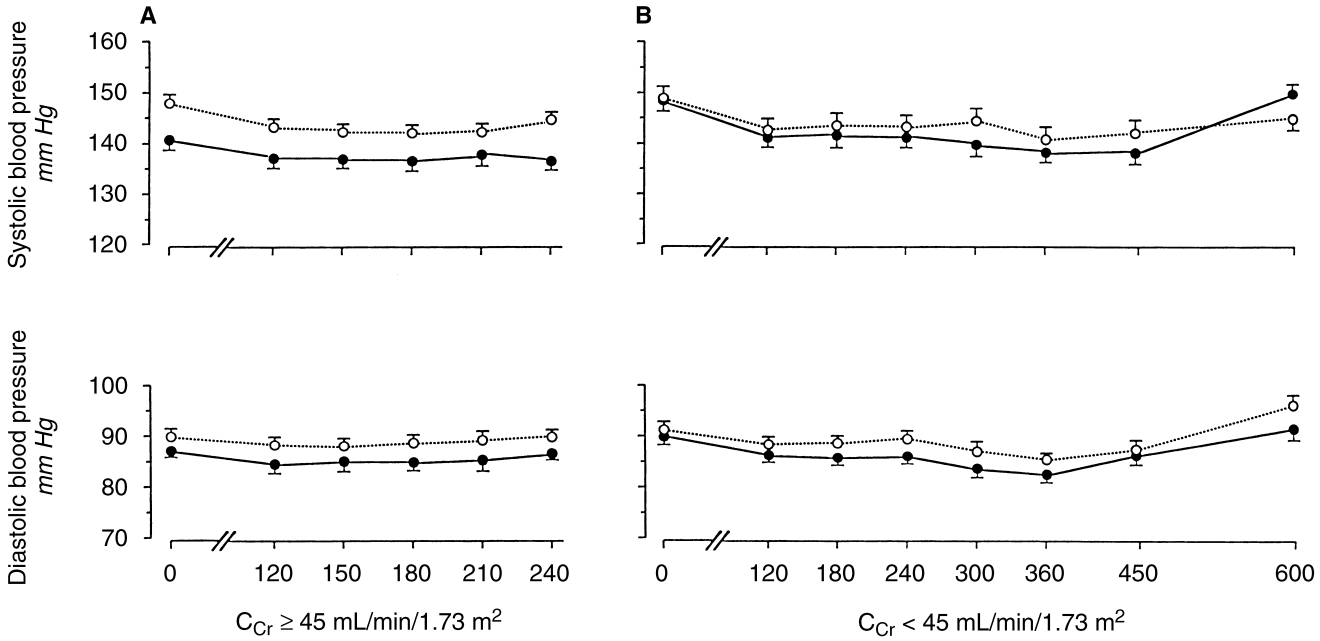

Fig. 1. Course of systolic and diastolic blood pressure (BP) monitored through glomerular filtration rate (GFR) measurements in 98 patients with baseline creatinine clearance ≥45/mL/min/1.73 m^2 (*A*) and in 65 patients with baseline creatinine clearance <45/mL/min/1.73 m^2 (*B*) on ramipril (■) or conventional (□) treatment. BP values are means ± SD of measurements taken at each time point during the entire study period, including baseline. Corresponding follow-up trough systolic and diastolic BPs are given in the text.

tional treatment, in terms of reduction in proteinuria, ΔGFR, and progression to ESRF (Fig. 2).

Correlations between trough, 0-minute, or 120-minute systolic/diastolic BP values and monitored systolic/diastolic BP values at baseline and follow-up are shown in Table 2. Of note, either at baseline or follow-up and regardless of the level of baseline creatinine clearance, both trough and 120-minute BPs correlated very well with monitored BP measurements, with correlation coefficients that were remarkably higher for systolic than for diastolic BP (Table 2).

Correlations of baseline or follow-up trough, 0-minute, 120-minute, and monitored systolic/diastolic BPs with ΔGFR are given in Tables 3 and 4. Of note, trough, 0-minute, 120-minute, and monitored systolic BPs correlated with ΔGFR better than the corresponding diastolic BPs, particularly at baseline and in the subgroup of patients with a baseline creatinine clearance <45 mL/min/1.73 m^2. However, among the different parameters considered, trough and 0-minute systolic BPs were the only parameters that significantly correlated with ΔGFR either at baseline or follow-up, in the entire study group and in both subgroups with baseline creatinine clearance < or ≥45 mL/min 1.73 m^2. In contrast, the 120-minute baseline and follow-up systolic BP measurements correlated with the GFR decline in patients with a creatinine clearance <45 mL/min 1.73 m^2, but not in those with less severe renal insufficiency. Of note, the baseline 120-minute diastolic BP did not correlate with the rate of GFR decline in both study groups. Follow-up diastolic BP values were always predictive of GFR decline, regardless of the timing of measurement.

Correlations between baseline trough, 0-minute, 120-minute, and monitored systolic/diastolic BP values and ΔGFR in ramipril and conventionally treated patients are given in Table 5. Of note, as compared with the correlations in the study group as a whole, the correlations between all the parameters considered (either at baseline and on follow-up) and ΔGFR remarkably improved in the ramipril-treated patients and, in contrast, weakened in the conventionally treated patients. Of interest, among different baseline measurements, only trough systolic BP retained a statistically significant correlation with ΔGFR in the conventional treatment group (Table 5).

Results of multivariate regression analyses, also including age, GFR, cholesterol, triglycerides and the 24-hour urinary protein excretion rate, between the independent (baseline and follow-up trough, 0-min, 120-min, and monitored diastolic BP) covariates and the risk of progression to ESRF are shown in Table 6. The analyses were not performed in patients with a creatinine clearance ≥45 mL/min/1.73 m^2, since only one event occurred in this subgroup. Of note, no baseline measurement of systolic or diastolic BP was significantly associated with the risk of ESRF. In contrast, the association between

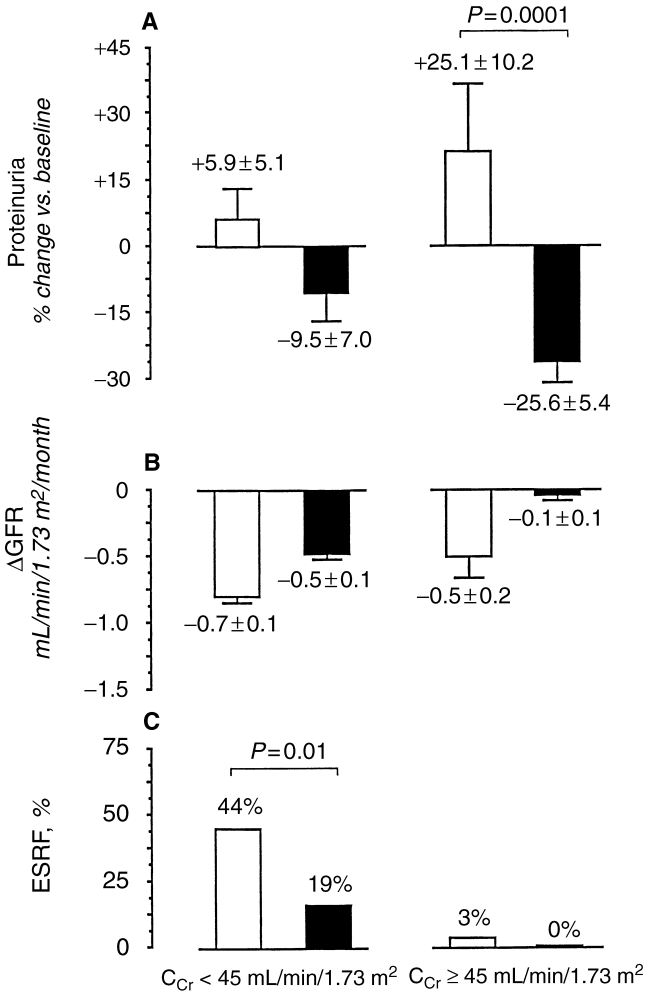

Fig. 2. Percent changes (mean ± SEM) in proteinuria versus baseline (*A*) and ΔGFR (*B*) and incidence of ESRF (*C*) on follow-up in patients with creatinine clearance ≥45 mL/min/1.73 m² (right panels) or with creatinine clearance <45 mL/min/1.73 m² (left panels) on ramipril (■) or conventional (□) treatment.

follow-up systolic or diastolic BP and risk of ESRF was highly significant for any of the considered measurements either in the entire study group or in the subgroup of patients with creatinine clearance <45 mL/min/1.73 m² (Table 6).

Multivariate regression analyses, including all of the parameters considered in the entire study group, between independent (baseline and follow-up trough, 0-min, 120-min, and monitored diastolic BP) covariates and risk of progression to ESRF were not possible in ramipril treated patients because the number of events was too limited. Of interest, despite the smaller sample size, trough follow-up (but not baseline) systolic and diastolic BP values retained an independent predictive value of ESRF even in conventionally treated patients [systolic RR (95% CI) = 1.07 (1.01 to 1.13), $P = 0.02$; diastolic RR (95% CI) = 1.49 (1.10 to 2.02), $P = 0.01$].

Table 2. Pearson correlation coefficients of trough, 0 minute, and 120 minutes of systolic/diastolic blood pressure with monitored systolic/diastolic blood pressure at baseline and on follow-up in the entire study group, and in the two subgroups of patients with baseline creatinine clearance ≥ or <45 mL/min/1.73 m²

	Systolic blood pressure		Diastolic blood pressure	
	Baseline	Follow-up	Baseline	Follow-up
Trough				
≥45 mL/min/1.73 m²	0.86	0.91	0.73	0.86
<45 mL/min/1.73 m²	0.84	0.86	0.77	0.77
Overall	0.85	0.87	0.75	0.80
0 min				
≥45 mL/min/1.73 m²	0.85	0.94	0.72	0.89
<45 mL/min/1.73 m²	0.82	0.88	0.78	0.82
Overall	0.83	0.90	0.75	0.85
120 min				
≥45 mL/min/1.73 m²	0.86	0.94	0.81	0.89
<45 mL/min/1.73 m²	0.85	0.95	0.84	0.89
Overall	0.86	0.95	0.83	0.89

$P = 0.0001$ for all the correlations considered.

Table 3. Correlations of baseline and follow-up trough, 0 minute, 120 minutes and monitored systolic blood pressure measurements with ΔGFR in the whole study group and in the two subgroups with baseline creatinine clearance < or ≥ 45 mL/min/1.73 m²

	Overall		C_{Cr} <45 mL/min/1.73 m²		C_{Cr} ≥45 mL/min/1.73 m²	
	r	*P* value	*r*	*P* value	*r*	*P* value
Baseline						
Trough	−0.34	0.0001	−0.35	0.0009	−0.32	0.01
0 min	−0.27	0.001	−0.23	0.03	−0.37	0.01
120 min	−0.23	0.006	−0.26	0.009	−0.06	0.69
Monitored	−0.32	0.0001	−0.33	0.0008	−0.25	0.09
Follow-up						
Trough	−0.39	0.0001	−0.36	0.0002	−0.41	0.005
0 min	−0.39	0.0001	−0.29	0.005	−0.51	0.0001
120 min	−0.35	0.0001	−0.35	0.0003	−0.29	0.05
Monitored	−0.41	0.0001	−0.39	0.0001	−0.42	0.003

r = Pearson correlation coefficient.

Table 4. Correlations of baseline and follow-up trough, 0 minute, 120 minutes and monitored diastolic blood pressures with ΔGFR in the whole study group and in the two subgroups with baseline creatinine clearance < or ≥ 45 mL/min/1.73 m²

	Overall		C_{Cr} <45 mL/min/1.73 m²		C_{Cr} ≥45 mL/min/1.73 m²	
	r	*P* value	*r*	*P* value	*r*	*P* value
Baseline						
Trough	−0.20	0.02	−0.26	0.02	−0.12	0.35
0 min	−0.25	0.003	−0.19	0.08	−0.38	0.004
120 min	−0.15	0.08	−0.18	0.10	−0.10	0.44
Monitored	−0.24	0.003	−0.26	0.01	−0.23	0.08
Follow-up						
Trough	−0.38	0.0001	−0.43	0.0001	−0.27	0.03
0 min	−0.32	0.0001	−0.24	0.03	−0.42	0.0008
120 min	−0.31	0.0002	−0.30	0.004	−0.28	0.03
Monitored	−0.36	0.0001	−0.36	0.0005	−0.34	0.008

r = Pearson correlation coefficient.

Table 5. Correlations of baseline and follow-up trough, 0 minute, 120 minutes and monitored systolic or diastolic blood pressures with ΔGFR in the ramipril and conventional treatment groups

	Systolic blood pressure				Diastolic blood pressure			
	Ramipril		Conventional		Ramipril		Conventional	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Baseline								
Trough	−0.43	0.0001	−0.28	0.02	−0.31	0.006	−0.12	0.34
0 min	−0.40	0.0003	−0.16	0.20	−0.37	0.001	−0.12	0.33
120 min	−0.36	0.001	−0.13	0.28	−0.18	0.10	−0.11	0.37
Monitored	−0.44	0.0001	−0.23	0.06	−0.31	0.006	−0.16	0.18
Follow-up								
Trough	−0.49	0.0001	−0.26	0.03	−0.44	0.0001	−0.28	0.02
0 min	−0.45	0.0001	−0.31	0.01	−0.32	0.004	−0.28	0.02
120 min	−0.39	0.0004	−0.29	0.02	−0.22	0.045	−0.32	0.007
Monitored	−0.37	0.0001	−0.33	0.007	−0.32	0.003	−0.33	0.006

r = Pearson correlation coefficient.

Table 6. Multivariate analysis of baseline and follow-up trough, 0 minute, 120 minutes and monitored systolic or diastolic blood pressure, and incidence of ESRF in the entire study group (Overall) and in the subgroup of patients with baseline creatinine clearance < 45 mL/min/1.73 m^2

	Systolic blood pressure				Diastolic blood pressure			
	Overall		C_{Cr} <45 mL/min/1.73 m^2		Overall		C_{Cr} <45 mL/min/1.73 m^2	
Variable	95% CI	*P* value	95% CI	*P* value	95% CI	*P* value	95% CI	*P* value
Baseline								
Trough	1.00 (0.97–1.03)	0.95	1.00 (0.97–1.04)	0.86	0.98 (0.94–1.01)	0.21	0.98 (0.95–1.02)	0.38
0 min	0.99 (0.96–1.02)	0.50	0.99 (0.96–1.01)	0.30	0.98 (0.95–1.02)	0.32	0.98 (0.95–1.01)	0.24
120 min	1.01 (0.98–1.04)	0.71	1.01 (0.98–1.04)	0.62	0.99 (0.95–1.03)	0.72	1.00 (0.96–1.04)	1.00
Monitored	1.02 (0.99–1.06)	0.16	1.02 (0.99–1.06)	0.17	1.01 (0.97–1.07)	0.58	1.02 (0.97–1.07)	0.50
Follow-up								
Trough	1.07 (1.02–1.11)	0.003	1.07 (1.02–1.12)	0.004	1.22 (1.09–1.38)	0.001	1.21 (1.07–1.37)	0.002
0 min	1.04 (1.01–1.07)	0.009	1.04 (1.01–1.08)	0.01	1.13 (1.04–1.22)	0.002	1.14 (1.04–1.25)	0.007
120 min	1.08 (1.04–1.13)	0.0002	1.08 (1.03–1.12)	0.0007	1.25 (1.10–1.42)	0.0006	1.25 (1.09–1.44)	0.001
Monitored	1.49 (1.14–1.94)	0.004	1.08 (1.03–1.12)	0.0009	1.25 (1.09–1.43)	0.001	1.23 (1.07–1.40)	0.003

Abbreviation is: 95% CI, 95% Confidence Interval.

DISCUSSION

In our study, regardless of the severity of basal renal insufficiency, either baseline and follow-up trough, 0-minute, and 120-minute systolic or diastolic BP values correlated to a similar extent with its corresponding monitored BP measurement. However, as compared to the 120-minute BP, the trough and 0-minute measurements—that is, morning pretreatment BPs—were stronger predictors of progression, and their predictability was remarkably good in particular in the ramipril-treated patients.

Overall, correlation analyses with ΔGFR found that systolic was more reliable than diastolic BP in predicting disease progression. Moreover, trough and time-0 systolic BP measurements were the only parameters that significantly correlated with GFR decline, both at baseline and on follow-up, in patients with more severe renal insufficiency and in those with more preserved renal function. In contrast, BP measured 120 minutes after effective therapy was administered was clearly the least predictive parameter. Indeed, in patients with a creatinine clearance ≥45 mL/min/1.73 m^2, the 120-minute systolic BP was the only parameter that did not correlate with the decline in GFR at either baseline or follow-up. In parallel, baseline 120-minute diastolic BP was the only parameter that never correlated with GFR decline in all patients, regardless of the level of renal insufficiency. In contrast, both trough and time 0 systolic and diastolic BP measurements had a predictive value that was quite close to that of the monitored BP. Of note, finding that the predictive value of trough and time 0 BP values was virtually identical demonstrates that the reliability of these two parameters is directly dependent on the timing (shortly before treatment administration), rather than on the modality (by a standard sphygmomanometer for trough and by an automatic device for time 0 BP) or the number (3 for trough and only 1 for time 0 BP) of measurements.

The predictive value of trough and time 0 systolic and diastolic BP measures was further corroborated by

results of multivariate analyses evaluating the relationships between the BP values and risk of progression to ESRF. In particular, these analyses clearly documented that, in addition to predicting a faster GFR decline, higher follow-up trough and time 0 BPs were also significant and independent predictors of an increased risk of progression to ESRF. The predictive value was evident both in the study group as a whole and in the subgroup of patients at the highest risk of progression because of a more severe renal insufficiency at study entry. These data clearly show that trough and time 0 BP measurements can be taken as reliable surrogates for monitored BP. In other words, BP measured shortly before treatment administration, regardless of the adopted procedure, is a reliable and practical indicator of overall BP control, and may serve to evaluate the patient's response to antihypertensive treatment while avoiding the need of time- and cost-consuming prolonged BP monitoring (which, however, remains the gold standard for BP measurement, since it more tightly reflects the overall BP to which target organs are exposed during the day). The reliability of this parameter is further confirmed by evidence that in patients with progressive chronic nephropathies and different degrees of renal dysfunction, the trough BP predicts disease outcome in the long term at least as precisely as the monitored BP measurements. In contrast, single measurements taken 120 minutes after treatment administration are not as reliable, to the extent that they predicted the risk of ESRF, but not the GFR decline in the long term. The lower predictive value of post-treatment as compared with pretreatment measurements may be due to the changes in BP that may occur at different times after treatment administration, in correspondence with the peak effect of different antihypertensive drugs. On the other hand, discovering that both the trough and 0 minute measurements were better predictors of outcome than the 120-minute values, and that their predictive values were comparable ruled out the possibility of a confounding effect of different technical procedures.

The failure to detect a predictive value for arterial BP when analyses were restricted to conventionally treated patients is consistent with previous evidence that in proteinuric chronic nephropathies, among a series of clinical and laboratory parameters, arterial BP is a relatively weak predictor of outcome, particularly as compared with proteinuria [16, 17]. Conceivably, on conventional treatment, patients with more proteinuria tend to have a faster progression even independently of the actual levels of BP control. In contrast, when patients are on effective antiproteinuric treatment—for instance, as in the present study, by an ACE inhibitor—the predictive value of proteinuria is almost entirely blunted, and arterial BP becomes the strongest predictor of progression. A suggested explanation is that in ramipril-treated patients, the predictive value of proteinuria was remarkably decreased (or fully blunted) because of the effect of ACE inhibition treatment on glomerular hemodynamics and barrier size–selectivity [18, 19]. Indeed, this effect, by limiting protein ultrafiltration (and proteinuria), prevents the sequence of events triggered by enhanced protein traffic that eventually contributes to progressive structural damage and renal dysfunction [1]. Thus, when the predictive value of proteinuria is blunted, arterial BP becomes the most important predictor of progression. These findings suggest that in the day by day management of patients with progressive chronic nephropathies, targeting the treatment to reach an optimal BP control is extremely important in maximizing the renoprotection conferred by chronic ACE inhibitor therapy. Actually, this approach can be remarkably effective in type 1 diabetics with overt nephropathy (Lewis E, Clinical Nephrology Symposium: Diabetes, the Kidney and More; *32nd Annual Meeting of the American Society of Nephrology*, Miami, 1999).

Another important finding of this study is that in all patients, even in those with more severe renal insufficiency, ramipril induced no acute reductions in arterial BP shortly after its administration. This may explain why it was so well tolerated and none of the patients enrolled in the REIN study required treatment withdrawal because of symptomatic hypotension [9–11].

In conclusion, to our knowledge this is the first study that prospectively analyzes the predictive value of different methods of BP measurement in patients with chronic progressive nephropathies. Within the limits of a study that was not formally designed to explore the reliability of different BP measurements and that may have the drawbacks of post hoc analyses, the study findings can be taken to conclude the following: (*1*) BP measured just before the administration of antihypertensive therapy, regardless of the measurement procedure, is a simple and precise indicator of daily BP control that may serve to guide antihypertensive therapy as well as predict disease outcome; (*2*) since systolic BP, in comparison to diastolic BP, is an even stronger predictor of outcome, antihypertensive therapy should be primarily aimed at normalizing systolic hypertension, even when diastolic BP is within ideal ranges; (*3*) single BP measurements taken shortly after treatment administration may not reliably reflect the real level of daily BP control and should not be used for monitoring the BP response to antihypertensive treatment either in routine clinical practice or in prospective controlled trials; (*4*) careful BP monitoring and effective antihypertensive treatment are extremely important in maximizing renoprotection, even in patients who are already on chronic ACE inhibitor therapy.

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